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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Masahiro Iwakura

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EXAMINER

PROUTY, REBECCA E

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/019,409	Applicant(s) IWAKURA, MASAHIRO	
	Examiner Rebecca E. Prouty	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 11-14 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Claims 7-10 have been canceled. Claims 1-6 and 11-14 are at issue and are present for examination.

Claims 1-6 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants' arguments filed on 10/19/05, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Li et al. and Recktenwald et al., in view of Lathrop et al. and Barnett et al. (WO96/30481). The rejection is explained in the previous Office Action.

Applicants argue that the prior art does not teach or suggest replacing all methionine and cysteine residues in a single protein. Rather, the combined disclosures teach the selective replacement of particular methionine or cysteine

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residues based on rational criteria and, therefore, teach away from replacing all methionine and cysteine residues in a single protein. Applicants go on to state that the Office does not identify where the cited references provide a suggestion or motivation to combine or modify them and that it appears that the Office is relying on knowledge generally available to one of ordinary skill in the art for the alleged motivation to combine or modify the references. Applicants then suggest the rejection engages in impermissible hindsight analysis to find the alleged motivation to combine or modify the references.

This is not persuasive as the rejection clearly relies on explicit disclosure by the cited references of the general motivation to improve the oxidative stability by proteins of interest by replacing one or more of the oxidative labile amino acids cysteine and methionine in both Li et al. and Recktenwald et al. The examiner relies on the knowledge of the skilled artisan only to extend this motivation specifically to why one would choose to modify **all** cysteine and methionine residues in opposition to selecting only some of the available residues for modification. Furthermore, the fact that a skilled artisan would consider replacing all such residues of a protein of interest (instead of selecting only particular residues) is further supported for example by Gillispe et al. (US Patent

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6,896,880). Gillispe et al. teach in columns 2-3 making variants of IL-8 in which one or more of the cysteine residues in the protein are replaced to produce variants having IL-8 activity and significantly higher stability than the wild-type polypeptide. Two of the specifically recited preferred embodiments of these variants are SEQ ID NOS:24 and 26 of Gillispe et al. in which all of the cysteine residues of the wild type IL-8 protein have been replaced. As such applicants arguments that the "accepted wisdom" in the art at the time of the invention was the selective replacement of only particular residues is not well taken as clearly the art did in fact teach both the selective replacement **and** replacing all residues without first predetermining which contributed most to the oxidative lability of the protein of interest. While Gillispe et al. was not previously cited this was merely because the cited art was considered to be substantially more relevant to the instant claims as the main disclosure of Gillispe is not drawn to making variants with improved stability (as the disclosures of all of Li et al, Recktenwald et al. and Barnett et al. clearly are). Gillispe et al. has been presented only to show that the selective replacement of only particular residues was not "accepted wisdom" in the art at the time of the invention as the art teaches examples of both strategies.

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Applicants next address the examiner's statement in the previous Office Action that "Applicants claimed methods amount merely to a systematic approach to accomplishing the goal of mutating all possible oxidatively labile residues in a manner in which some activity of the enzyme can be maintained. Both applicants "combined mutation method" i.e., determining individually the most active replacements at each position individually and then combining these together and applicants "stepwise method", i.e., further mutagenizing a previously selected mutant, of modifying would have been obvious to a skilled artisan given a desire to mutate any group of several amino acids in a protein while maintaining activity and both strategies have been used in the art for multiple mutagenesis experiments." By arguing that 1) a group of several amino acids, wherein the amino acids have the specific characteristic of containing a sulfur atom is not the same as a group of several amino acids and the claims are directed to the mutagenesis of all sulfur atom-containing amino acids, not any amino acids; and 2) directed evolution as later mentioned by the examiner is a method of random mutagenesis while applicants claims are drawn to methods of mutating specific amino acids. However, applicants arguments take the examiners comments out of context and fail to address how these statements relate to the instant

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rejection. First it is noted that the statement "given a desire to mutate any group of several amino acids in a protein ..." in the examiner's action was included after first exhaustively discussing why a skilled artisan would have found it obvious to mutate methionine and cysteine residues specifically. Thus the rejection as a whole does not argue that mutagenesis of any group of amino acids would have been obvious but that the mutagenesis of cysteine and methionine residues would have been obvious. Secondly the reference to directed evolution methods by the examiner was made only to show that the art would consider mutagenesis methods which involve **multiple rounds** of mutagenesis (whether random as in directed evolution or site-specific as in the claimed methods) followed by a selection step to be a reasonable means of producing a mutant with desired properties and thus that the inclusion of such multiple rounds in the claimed methods would not have motivated a skilled artisan to not select the instant method to accomplish the desired goal. For all the reasons discussed above the rejection is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this

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action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Rebecca Prouty
Primary Examiner
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